

January 14, 2004

Timothy Adams, Ph.D.
Technical Contact
Eastman Chemical Company
100 North Eastman Road
Kingsport, TN 37662

Dear Dr. Adams:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for Methyl 4-Formylbenzene posted on the ChemRTK HPV Challenge Program Web site on August 19, 2003. I commend Eastman Chemical Company for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that Eastman Chemical Company advise the Agency, within 60 days of this posting on the Web site, of any modifications to its submission. Please send any electronic revisions or comments to the following e-mail addresses: oppt.ncic@epa.gov and chem.rtk@epa.gov.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

-S-

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: W. Penberthy
M. E. Weber

EPA Comments on Chemical RTK HPV Challenge Submission: Methyl 4-Formylbenzoate

Summary of EPA Comments

The sponsor, Eastman Chemical Company, submitted a test plan and robust summaries to EPA for methyl 4-formylbenzoate, CAS No. 1571-08-0 on July 27, 2003. EPA posted the submission on the ChemRTK HPV Challenge Web site on August 19, 2003. Information was also provided for several analogs: terephthalic acid, benzaldehyde, methyl benzoate, and dimethyl terephthalate.

EPA has reviewed this submission and has reached the following conclusions:

1. Analog Justification. EPA agrees with the submitter's analogs for the health effects endpoints and, with the exception of terephthalic acid, for the ecological effects endpoints.
2. Physicochemical Properties. The submitter needs to provide measured vapor pressure and water solubility data.
3. Environmental Fate. The submitter needs to include the input values used in its fugacity model in the robust summary. EPA recommends that the submitter use the Level III model instead of the level I model for the fugacity calculation. The submitter needs to address some deficiencies in the biodegradation robust summary.
4. Health Effects. All endpoints have been adequately addressed for the purposes of the HPV Challenge Program.
5. Ecological Effects. All endpoints have been adequately addressed for the purposes of the HPV Challenge Program.

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

EPA Comments on the Methyl 4-formylbenzoate Challenge Submission

Analog Justification

EPA agrees with the submitted analogs for methyl 4-formylbenzoate for the health effects endpoints. In general, the presentation was unfocused and too long. For example, information on hydrolysis at an acidic pH was omitted although measured data were evidently available in the reference cited (Hoffman, 2003). The most relevant data in a series of hydrolysis experiments on alkyl benzoates, the plasma half-lives for methyl benzoate, were not included, yet, it appears that they were reported in Nielson and Bundgaard (1987). In general, the information provided on hydrolysis, especially under conditions found in gastric juice, is poorly addressed. Important questions about the rate of hydrolysis remain unanswered.

Most of the analog information supplied was considered relevant for ecological effects endpoints. Terephthalic acid data were not considered suitable for the following reasons:

- The submitter reported that the estimated half-life at pH 7 and 25°C was 3286 hours (136.9 days; p.14, robust summary) for methyl 4-formylbenzoate, which suggests that significant hydrolysis of the ester to the acid is not likely to occur under the conditions of an acute aquatic toxicity test.

- Acids such as terephthalic acid become charged species under the conditions of aquatic toxicity testing, with different toxicological behavior from esters such as dimethyl terephthalate and methyl 4-formylbenzoate.

Test Plan

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility)

The data provided by the submitter for melting point, boiling point, and partition coefficient are adequate for the purposes of the HPV Challenge Program.

Vapor pressure. The data provided by the submitter are not adequate for the purposes of the HPV Challenge Program. The submitter estimated a vapor pressure of 0.88 Pa at 25 °C using MPBPVP v1.40. According to HPV Guidelines, vapor pressures estimated to be $>10^{-5}$ Pa ($>7.5 \times 10^{-8}$ mm Hg) need to be measured (OECD TG 104). Data provided for related chemicals dimethyl terephthalate, methyl benzoate and benzaldehyde suggest that the vapor pressure of methyl 4-formylbenzoate is greater than 10^{-5} Pa. The submitter needs to provide measured data for methyl 4-formylbenzoate following OECD guidelines. Measured data from published sources are acceptable, as long as the submitter identifies the reference.

Water solubility. The submitter estimated a water solubility of 3,136 mg/L at 25 °C using WSKOW v1.40. Estimated water solubility values are generally not acceptable for the purposes of the HPV Challenge Program. The submitter provided water solubility data for two structural analogs: 15 mg/L at 10 °C and 19 mg/L at 25 °C for terephthalic acid, and 28.7 mg/L at 20 °C and 37.2 mg/L at 25 °C for dimethyl terephthalate. These data suggest that methyl 4-formylbenzoate will have a water solubility on the order of 20 mg/L. Since the water solubility estimate is >1 µg/L, the submitter needs to provide measured water solubility data for methyl 4-formylbenzoate following OECD TG 105. Measured data from published sources are acceptable, as long as the submitter identifies the reference.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity)

The data provided by the submitter for photodegradation, stability in water, and biodegradation are adequate for the purposes of the HPV Challenge Program.

Fugacity. The sponsor estimated the fugacity of these chemicals using a level I model. Although EPA had previously recommended level I, this model is somewhat limited. EPA now recommends the use of level III, which provides a more rigorous level of analysis. EPA believes that values based on a level III fugacity model are more realistic and useful for estimating a chemical's fate in the environment. The submitter needs to recalculate its fugacity model using measured water solubility and vapor pressure data, and to incorporate in the robust summary all input values used.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity)

Adequate data are available to satisfy the acute, repeated-dose, genetic, and reproductive/developmental toxicity endpoints. With the exception of acute toxicity, EPA agrees with the reliance on information provided by analogs. The submitter needs to address a few deficiencies in the robust summaries.

Ecological Effects (fish, invertebrates, and algae)

Data for dimethyl terephthalate and methyl benzoate are adequate to satisfy the endpoint for fish, data for dimethyl terephthalate, methyl benzoate, and benzaldehyde for invertebrates, and data for dimethyl terephthalate and benzaldehyde for algae.

Specific Comments on the Robust Summaries

Generic comments

The format for reporting information from individual studies is misleading. The “header” for each study identifies the sponsored HPV chemical and is followed with a CAS No. for that chemical. However, there is no indication in the header whether the summary that follows is on the HPV chemical or an analog. The identity of the test substance is often provided in a “remarks” section but this format is variable (see pages 90 and 91 of the robust summaries) and in some cases, the reader does not find out until the end of the summary that the test substance used was not the HPV chemical. On page 96, the test substance is unclear since two chemicals are identified in the summary; however, this study is coded as unreliable and could be omitted.

A citation for the WHO document (Technical Information Series, 2001) referred to on p. 25 was omitted in the list of references and should be added.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity)

Biodegradation. The submitter needs to provide information on the purity of the substance and total contact time in its biodegradation robust summary for methyl 4-formylbenzoate.

Health Effects

All summaries for health effects studies were missing the purity of the test material and the CAS Nos. for analogs.

Developmental Toxicity. A robust summary for a developmental toxicity assay in rats exposed to particulate terephthalic acid by inhalation on gestational days 6-15 was missing information on the test atmosphere, including the particle size distribution and the relationship of the highest tested concentration to the highest attainable concentration.

Ecological Effects

Fish. Information missing from one or more of the robust summaries of acute toxicity of dimethyl terephthalate, methyl benzoate, and benzaldehyde to fish included test substance purity, test type, concentrations tested/responses, fish specifications, water quality parameters, control /response, statistical methods used, and whether or not the reported LC₅₀ values were based upon measured or nominal concentrations.

The robust summaries for the studies of methyl benzoate in *Lepomis macrochirus* reported that “Undissolved test substance was noted at the two highest concentrations.” The submitter needs to discuss the potential mechanisms for the formation of the salt/undissolved test substance and whether or not valid aquatic toxicity studies can be conducted in the absence of analytical monitoring in light of the fact that no water solubility data were reported. The submitter also needs to discuss whether or not the presence of undissolved test substance at 40 and 80 mg/L may have affected the derivation of the LC₅₀ value since the test substances may have reacted with other components of the test systems, resulting in reduced concentrations of the test compounds over the course of these aquatic studies.

Invertebrates. Information missing from one or more of the robust summaries of acute toxicity of dimethyl terephthalate, methyl benzoate, and benzaldehyde to *Daphnia magna* included test substance purity, duration of exposure, concentrations tested/responses, control/response, animal specifications, water quality parameters, statistical methods used, and whether or not the reported EC₅₀ values were based upon measured or nominal concentrations.

Algae. Information missing from one or more of the robust summaries of acute toxicity of dimethyl terephthalate, and benzaldehyde to green algae included test substance purity, effects seen at each concentration tested (e.g., whether or not the identified growth inhibition took place at the highest concentration), control/response, statistical methods used, and whether or not the reported EC₅₀ values were based upon measured or nominal concentrations and the submitter needs to provide a 72-hr EC50 value.

Followup Activity

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.